REMARKS

The Applicants have canceled claim 9 and added claims 16-18. They address the rejections of the Office Action as follows.

The rejection of claims 1-3 and 6-9 under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 1-3 and 6-9 under 35 U.S.C. § 112, first paragraph, arguing that the specification enables a method of treating Parkinson's disease and Alzheimer's disease, but does not enable a method of treating all neurodegenerative conditions.

The Applicants have amended the claims such that they are now directed to a method of treating Parkinson's disease and Alzheimer's disease, thus mooting the rejection. The Applicants respectfully request that the Examiner withdraw it.

The rejection of claims 3 and 10-15 under § 112, first paragraph

The Examiner rejected claims 3 and 10-15 under § 112, first paragraph, arguing that the specification does not enable a method of preventing death or degeneration of neurons projecting to or from the areas of the brain recited in the claims. The Applicants disagree for the same reasons they state in their response of September 11, 2007. The Applicants reproduce the substance of their response here.

To prevent death or degeneration of neurons, the specification teaches that one should administer the compounds of the invention. As with the previous enablement rejection, the Examiner's principal objection is that the specification lacks sufficient examples; she argues that such examples are necessary because

> The term "prevention" or "preventing" is synonymous with "curing" and both circumscribe [sic] methods of treatment having absolute success. Since absolute success is not as of yet reasonably possible with most diseases/disorders, the specification is viewed as lacking an adequate enablement of where Parkinson's disease may be actually prevented.

Office Action, at 7. This is an unreasonable construction of the term “prevent.” While prevention encompasses methods achieving “absolute success” and “cure,” there is nothing in the specification to indicate that the term includes *only* such methods. The term “prevent,” as used here, means to “delay the onset of,” or “slow the progression of.” Indeed, were one to adopt the Examiner’s extraordinary construction, and require absolute certainty of outcome, then it could be said that there is no such thing as “prevention” – for what does medical science address with “absolute success?” We should believe, then, that the FDA has been misguided in its labeling for all of the drug products indicated for the “prevention of” diseases, such as BONIVA®, which is “indicated for the treatment and prevention of osteoporosis,” a disorder, like neurodegenerative disorders, that is progressive, or “FLUMIST,®” which is “intended for active immunization for the prevention of influenza.”

The Examiner again objects that the specification does not provide sufficient guidance for practicing the claimed method, but, again, she does not explain what guidance is required. To prevent death or degeneration of neurons, one administer the compounds of the invention – what is lacking in this method that requires undue experimentation to discover the Examiner does not say, and without such an explanation, the Examiner cannot have met her burden to show that the claims are not enabled.

For the foregoing reasons, the Applicants respectfully request that the Examiner withdraw the objection under § 112, first paragraph.

The rejection of claim 9 under § 112, second paragraph

The Examiner rejected claim 9 under § 112, second paragraph, arguing that the claim is indefinite. The Applicants respectfully disagree. The Applicants have in any event canceled claim 9, thereby mooting the rejection.

The rejection of claim 1-3 and 5-9 under 35 U.S.C. § 103(a)

The Examiner rejected claims 1-3 and 5-9 under 35 U.S.C. § 103(a), arguing that the claims are obvious in view of the Arnsten, O'Rourke, and Allergan references. In this paper the Applicants submit additional evidence why this rejection is improper.

The Examiner's argument is as follows:

- Arnsten discloses that clonidine caused memory improvements in animal models of dementia;
- O'Rourke "teaches there is potential for the use of alpha-2 adrenergic agonists in treating Alzheimer's disease," Office Action, at 11;
- The Allergan reference discloses AGN 197075.

The Arnsten reference is unremarkable. It does not stand for the proposition that clonidine can be used to treat neurodegenerative conditions.

First, Arnsten does not use an animal model of dementia or neurodegeneration. The experimental subjects are normal, aged animals:

> If loss of catecholamines contributes to age-related cognitive decline, then pharmacological treatments that facilitate their transmission may ameliorate the cognitive deficits. This hypothesis was investigated by examining the effects of catecholaminergic agonists on cognitive performance in five female rhesus monkeys ranging from 17 to over 30 years of age.

Arnsten, at 1274. There is no evidence that any of the animals have Alzheimer's disease, Parkinson's disease, or any other neurodegenerative condition. The authors were investigating "age-related cognitive decline," and their use of aged – but normal – animals is consistent with this purpose. Hence, we are left with nothing more than the observation that clonidine improves performance on a certain memory-related task in normal animals. What effect clonidine has on animals with neurodegenerative conditions is untested. Arnsten does not address this question.

The premise of the Office Action that clonidine will have any effect in animals with neurodegenerative conditions is therefore nothing more than speculation.

Second, Arnsten provides no evidence that clonidine is effective in protecting neurons of the substantia nigra, ventral tegmental area, or locus coruleus, areas of the brain that experience significant neuronal loss in Alzheimer's disease and Parkinson's disease. Indeed, Arnsten shows precisely the opposite: that clonidine does not affect those areas, but affects the principal sulcul region, instead:

> The results of the depletion studies are consonant with clonidine acting at super-sensitive, postsynaptic α_2 receptors in the principal sulcal cortex. This idea was tested further by examining whether clonidine would remain effective in young adult animals in which the post-synaptic α_2-receptor population in the principal sulcal region had been removed surgically . . . in contrast with the aged [i.e., normal] monkeys, clonidine failed to improve the performance of these animals.

Arnsten, at 1275-1276. Neuronal loss in the substantia nigra, ventral tegmental area, or locus coruleus are associated with Alzheimer's disease and Parkinson's disease. See, e.g., Zarow et. al, Arch. Neurol. 60:337-341 (2003) ("For both AD and PD the greatest neuronal loss was found in the LC [locus coruleus]."); Attems et. al, Acta Neuropathol., 113(1):53-62 (2007) ("neuronal loss in SN [substantia nigra], partly related to tau lesions, is a major pathological substrate of EPS [extra-pyramidal symptoms] in AD."); Mann et. al, J. Neurol. Neurosurg. Psychiatry, 50(3):341-4 (1987) ("In 15 patients with Alzheimer's disease . . . there was severe atrophy, neurofibrillary degeneration and loss of pigmented dopaminergic nerve cells from ventral tegmental area whereas nerve cells in neighbouring substantia nigra were much less affected in all three respects.") (all of these references are attached hereto). Hence, Arnsten suggests that clonidine fails to target those areas of the brain that are most effected in Alzheimer's disease and Parkinson's disease. For this reason, as well, there is no reason to believe that clonidine has any effect on treating neurodegenerative conditions.

Even assuming that Arnsten suggests that clonidine may be used to treat neurodegenerative disease (which it does not), the reference still does not defeat patentability, as it is directed to an alpha-2 pan-agonist, and tells us nothing about what effects one could expect of the alpha-2B and alpha-2B/2C selective agonists of the invention. The Examiner has not provided any evidence why one of ordinary skill in the art would substitute an alpha 2B or alpha 2B/2C selective agonist for the alpha-2 pan agonist of Arnsten, or why one would reasonably expect the compounds to have the same properties.

It is inappropriate to attribute to the alpha-2B and alpha-2B/2C agonists of the invention the properties of clonidine. Clonidine binds alpha-2A, alpha-2B, and alpha-2C receptors; according to Arnsten and Ramos, "the α2A receptor subtype may be the most critical for cognitive enhancement." Arnsten and Ramos, Pharmacol. Ther. 113(3):523–536 (2007); see also Galeotti et al., Behav. Brain Res. 153(2):409-17 (2004). There are differences in other contexts, as well. For example, Stone, et al., J. Pharmacol Exp Ther. 323(3):899-906 (2007), claim that "Most alpha2 [adrenergic receptor] agonists require alpha(2A) [adrenergic receptor] activation to produce antinociception and opioid synergy." Höcker et al., Anesthesiology 109(1):95-100 (2008) found that meperidine, a compound for treating shivering, modulates the thermoregulatory response of alpha-2B and alpha-2C knock-out mice but has no effect on alpha-2A knock-out mice. Yoshitomi et al., Anesth. Analg. 107(1):96-101 (2008) showed that an alpha-2 pan antagonist but not an alpha-2B and 2C antagonist blocked the action of dexmedetomidine, suggesting that dexmedetomidine acts via alpha-2A receptors. Hence, that clonidine has certain activity does not suggest that the agonists of the invention – which are selective for different receptors – will have the same activity.

The Examiner cites O'Rourke for the proposition that "there is potential for the use of alpha-2 adrenergic agonists in treating Alzheimer's disease." The Examiner continues, that "[t]herefore, one of ordinary skill in the art would have [a] reasonable expectation of treating Alzheimer's disease with AGN-197075, an alpha-2 agonist."

Office Action, at 11. But the Examiner provides no evidence that the O'Rourke reference stands for what she alleges; her allegation that O'Rourke "teaches there is potential for the use of alpha-2 adrenergic agonists in treating Alzheimer's disease" represents the entirety of the Examiner's observations regarding O'Rourke; about that reference she states no more. The reference discloses the results of *in vitro* radioligand binding assays using CHO-C10 cells, neonatal rat lung, OK cells, and bovine pineal gland; what the reference teaches about the "use of alpha-2 adrenergic agonists in treating Alzheimer's disease" the Examiner does not say – and neither does the reference.

For the foregoing reasons, the Applicants respectfully request that the Examiner withdraw the rejection under § 103.

The Provisional Double-Patenting Rejection

The Examiner rejected claims 1-3 and 7 for obvious-type double patenting in view of copending application no. 10/881,761. The Applicants respectfully disagree that the rejection is proper.

The co-pending application is directed to methods of treating Parkinson's disease and Alzheimer's disease by administering brimonidine, an alpha-2 pan agonist. The present application, in contrast, is directed to alpha-2B and alpha-2B/2C agonists. As explained above, it is improper to infer that because alpha-2 pan agonists have certain activity, alpha-2B and alpha-2B/2C agonists will have the same activity. For this reason, the Applicants respectfully request that the Examiner withdraw the double patenting rejection.

The undersigned authorizes the Director to charge any fees required or necessary for the filing, processing or entering of this paper or any of the papers transmitted with it, and to refund any overpayment, to deposit account 01-0885.

Respectfully submitted,

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